



The anticancer properties of harmine and its derivatives

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Received: 22 November 2023 / Accepted: 20 May 2024 / Published online: 17 September 2024
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Abstract This review aims to provide information about the anticancer potential of harmine, a β -carboline alkaloid that was initially isolated in 1847 from the seeds and roots of *Peganum harmala* L. Various studies have revealed that it possesses a wide range of therapeutic qualities, including anti-inflammatory, antibacterial, antiviral, antidiabetic, and, most notably, anticancer effects. This review discusses the anticancer capabilities of harmine and its derivatives against malignancies such as breast cancer, lung cancer, gastric cancer, colon cancer, glioblastoma,

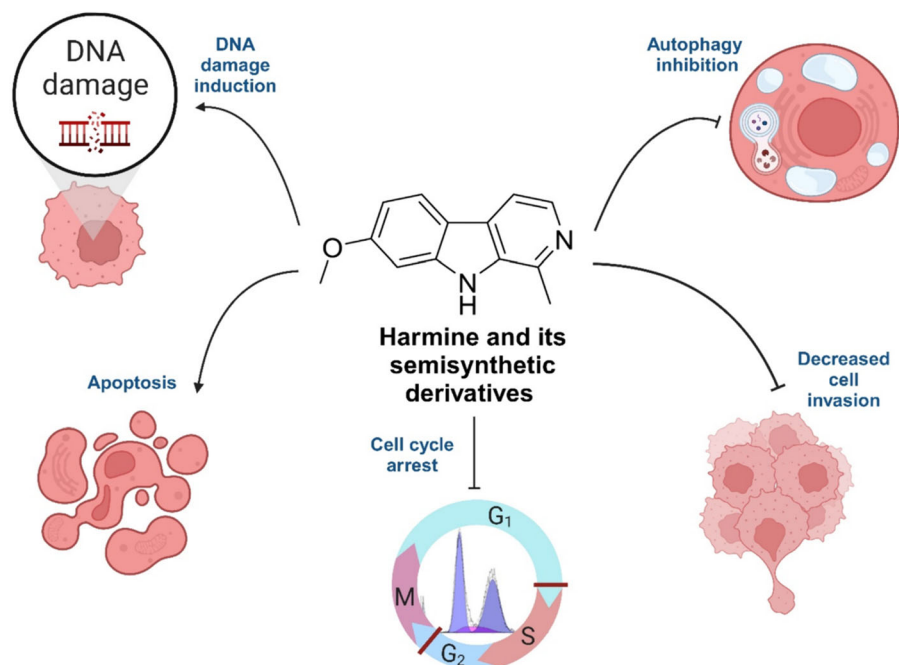
neuroblastoma, liver cancer, pancreatic cancer and thyroid cancer. Harmine uses mechanisms such as apoptosis and angiogenesis inhibition to fight cancer cells. It also influences the cell cycle by inhibiting specific cyclin-dependent kinases and slowing tumor cell proliferation. Synergistic effects have also been observed when harmine is used in combination with other anticancer medications. Harmine has the potential to be a potent anticancer medication that can help in the fight against cancer.

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Graphical abstract



Keywords Harmine · Alkaloids · Cancer · Biological activity · Cytotoxicity · Semisynthetic derivatives

Abbreviations

BMI	Body Mass Index
CDK	Cyclin-dependent kinases
CI	Combination index
COX-2	Cyclooxygenase 2
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DSB	Double strand break
DYRK1A	Dual-specificity tyrosine-phosphorylated and regulated kinase 1A
EGFR	Epidermal growth factor receptor
EMT	Epithelial-to-mesenchymal transition
FAP	Familial adenomatous polyposis
GSK-3	Glycogen synthase kinase 3
GSLC	Glioblastoma stem-like cells
HDAC	Histone deacetylase
HMH	Harmine hydrochloride
HPLC	High-performance liquid chromatography
HPV	Human papillomavirus

HR	Homologous recombination
IL-2	Interleukin-2
MAPK	Mitogen-activated protein kinases
MMP	Matrix metalloproteinases
mTORC1	Mammalian target of rapamycin complex 1
NB	Neuroblastoma
NF-κB	Nuclear Factor kappa B
NHEJ	Nonhomologous end joining
NO	Nitric oxide
NSCLC	Non-small cell lung cancer
PARP	Poly (ADP-ribose) polymerase
PI3K	Phosphatidylinositol-3-kinase
PTEN	Phosphatase and tensin homolog
Raf	Rapidly accelerated fibrosarcoma (Raf) kinase
Ras	Rat sarcoma (Ras) protein
RK	Extracellular-signal-regulated kinases
SAR	Structure-activity relationship
SRB	Sulforhodamine B
TAZ	Transcriptional coactivator with PDZ-binding motif
TCF/LEF	T-cell factor/lymphoid enhancer factor
THH	Tetrahydroharmine

TLC	Thin layer chromatography
TRAP	Telomerase repeated amplification procedure.
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

Introduction

A hallmark of cancer is the rapid proliferation of abnormal cells that exceed their typical boundaries, invade adjacent body structures, and eventually spread to distant organs, a phenomenon referred to as metastasis. The primary cause of mortality among cancer patients is the widespread occurrence of metastases. Synonymous terms for this include neoplasms and malignant tumors. According to the World Health Organization (WHO), cancer stands as the foremost global cause of death, with approximately 10 million fatalities in 2020, equating to about one in every six deaths. The most common types include breast, lung, colon, rectum, and prostate cancers. Contributing factors to nearly one-third of cancer-related deaths encompass tobacco use, high body mass index (BMI), alcohol consumption, insufficient intake of fruits and vegetables, and a lack of physical activity. In low- and lower-middle-income nations, infections such as human papillomavirus (HPV) and hepatitis contribute to approximately 30% of cancer cases. Early detection and appropriate treatment offer the potential for successful management of many tumors (WHO 2022).

The discovery of new antitumor agents from natural resources is currently gaining popularity. The natural β -carboline alkaloid harmine, along with its related compounds tetrahydroharmine (THH) and harmaline, is present in various plants across the globe. These plants include the seeds and roots of Syrian rue (*Peganum harmala* L.), which is a medicinal plant utilized in North Africa, the Middle East, and Central Asia (Moloudizargari et al. 2013; Patel et al. 2012). Indeed, harmine and harmaline were initially extracted and identified from the seeds and roots of *Peganum harmala* L. in the 1840s (Moloudizargari et al. 2013; Ott 1994; Patel et al. 2012). Harmine has been reported to have anticancer (Shabani et al. 2015), antioxidant (Choi et al. 2004; Salman et al. 2016), antidepressant (Hamid et al. 2017), anti-inflammatory

(Hara et al. 2013), and neuroprotective (Herreraiz 2012) properties. Over the last decade, research has revealed that harmine has powerful cytotoxic and antiproliferative activities. Nonetheless, due to the severity of neurotoxicity effects seen in animal models, harmine's use in clinical settings has been hindered (Chen et al. 2005; Li et al. 2015).

Several researchers have synthesized harmine derivatives to acquire compounds which are more effective against the activities of tumors and cause less neurotoxicity than harmine (Zhang et al. 2020a). By means of altering the substituents at the β -carboline nucleus' positions C1, N2, C3, C7, and N9, harmine derivatives were created (Domonkos et al. 2015). Additionally, results from in vitro and in vivo studies, show that by making modifications of harmine at positions C2, C7, and N9, brought about an exceptional improvement in the anticancer properties of harmine and also showed a remarkable decrease in the side effects. This is all as a result of the alterations done at the positions mentioned previously which caused cancer cells to specifically take up more of the drug than the normal cells (Li et al. 2015). Comparing harmine derivatives with harmine, it was shown that they had comparable pharmacological effects, including those that were neuroprotective, anticancer, antiparasitic, and antiviral. These effects were also associated with increased activity and decreased neurotoxicity (Zhang et al. 2020a).

This article reviews the anticancer properties of harmine and its derivatives, along with the mechanisms of action involved.

Sources of harmine

Harmine (1, $C_{13}H_{12}N_2O$, Fig. 1) is found in a wide variety of plants around the world (Zhang et al. 2015). *Peganum harmala* L. is where harmine was first extracted from and it was previously used for traditionally as a powerful natural medicine due to its abortion-inducing properties, psychedelic, hypothermic and emmenagogue qualities. Emmenagogues are herbs that improve blood flow to the uterus and pelvis are frequently used to induce menstruation in women who do not have it for non-pregnancy-related causes, such as disorders from hormonal origins or disorders such as oligomenorrhea (Filali et al. 2015). While *P. harmala* was previously classified as a member of the

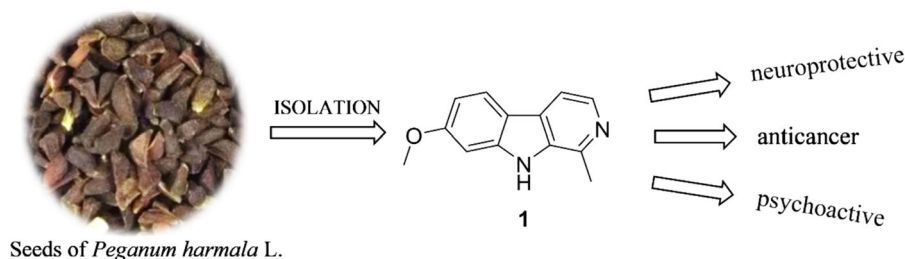


Fig. 1 Main source, structure and reported biological activity of harmine (1)

Zygophyllaceae family, it is now recognized as a member of the Nitrariaceae family (Filali et al. 2015). In Northwest China, *P. harmala* extracts from seeds have been used for many years to treat gastrointestinal cancers and malaria (Cao et al. 2013). Moreover, plants containing harmine, such as *P. harmala* or *Banistereopsis caapi* (Spruce ex Griseb.) C.V.Morton, are key ingredients in the preparation of the potent hallucinogenic drink ‘Ayahuasca’. This beverage plays an integral role in native shamanistic rituals in South America (Rivier and Lindgren 1972). In recent years, however, it has also become a lucrative attraction for many adventure seekers.

The seeds of *P. harmala* (Fig. 1) are the most common source for obtaining harmine, which is typically isolated using standard phytochemical techniques from the dried material. This material is often processed into either an ethanolic (Gaviraj et al. 1998; Shao et al. 2013; Siddiqui and Kemal 1964) or methanolic summary extract (Al-Shamma et al. 1981; Gohar et al. 1994; Wang et al. 2015a). Liquid-to-liquid extraction is used to prepare the alkaloidal fraction, after which harmine is isolated using chromatographic techniques. These methods may involve preparative high-performance liquid chromatography (HPLC), thin layer chromatography (TLC), or column chromatography (Fang et al. 2019; Shao et al. 2013).

One of the earliest studies, conducted in 1947, detailed the isolation process from *P. harmala* seeds. The seeds were subjected to light petroleum extraction, charcoal treatment, and alcoholic ammonia extraction. The resultant material was then treated with pyridine, resulting in harmine crystallization (Ovejero 1947). Using a multiple-layer coil planet centrifuge, an interesting isolation technique was investigated. Using this technique, 554 mg of harmine could be extracted from 1.2 g of the crude alkaloid extract, which was obtained from 1 kg of dried seeds

extracted with 95% ethanol and purified by acid–base extraction (Wang et al. 2008). Various efficient and economical methods of harmine isolation from *P. harmala* seeds have been investigated, including a metal-mediated method involving mercury (II) ions (Munir et al. 1995). There is also a patent detailing the extraction from different parts of *P. harmala*, underlining the significance of effective harmine isolation (Herraiz Tomico et al. 2011).

Upper parts of the *P. harmala* plant were used for isolation in 1957, extracted with 80% isopropanol. Following acid–base liquid–liquid extraction, the mixture was shaken with chloroform, leading to harmine isolation from the alkaloid mixture (Koret-skaya 1957). Later, in 1974, harmine was extracted from *P. harmala* stems in Saudi Arabia (Muhtadi et al. 1974), and from both the seeds and leaves a few years later (Jado et al. 1979). In 2012, harmine was isolated from the leaves and twigs of the plant by percolating with dichloromethane, conducting liquid–liquid extraction, and semi-preparative HPLC (Grabher et al. 2012). Harmine was also extracted from *P. harmala*’s aerial portions in a study conducted in 2022, which were extracted with 75% ethanol, followed by acid–base liquid–liquid extraction to dichloromethane, and further processed by column chromatography and HPLC (Zhang et al. 2022). Additionally, the methanolic extract of the roots of *P. harmala* was also found to possess harmine (Ayoob et al. 2017).

Another species of the genus *Peganum*, *P. nigellastrum* Bunge, was discovered to contain harmine. It was extracted from its aerial parts (Ma et al. 2000), roots (Babalakova et al. 2011; Ma et al. 2008), and seeds (Zheng et al. 2009).

In 1998, harmine was acquired from the seeds of *Peganum multisectum* (Maxim.) Bobrov (Duan et al. 1998b) and, soon after, from an ethanolic extract of its

aerial parts (Duan et al. 1998a). Harmine was isolated from *P. multisectum* again a few years later (Liu 2011). The aerial portions of *P. multisectum* plants grown in Mongolia were examined further in 2017 for harmine isolation through column chromatography (Javzan et al. 2017).

The first convincing evidence of harmine in *B. caapi* dates back to 1939 when it was found in the stems, leaves, and roots (Chen and Chen 1939). An extensive study of alkaloids present in the Ayahuasca drink further confirmed the presence of harmine in the stems of *B. caapi*. The isolation was achieved through maceration in methanol and standard acid–base procedures (Rivier and Lindgren 1972). In 1972, harmine was also isolated from *B. caapi* in another study; however, the plant was referred to by its synonym, *Banisteriopsis inebrians* C.V.Morton (Saa Rodriguez 1972). A lyophilized water extract from a large branch of the *B. caapi* cultivar ‘Da Vine’ was subjected to reverse phase column chromatography to yield several fractions. These were further separated by TLC, resulting in the isolation of several alkaloids, including harmine (Samoylenko et al. 2010). A recent study from 2022 also confirmed the abundant presence of harmine in a *B. caapi* sample (Santos et al. 2022). Harmine was also extracted from the stems and leaves of *Banisteriopsis muricata* (Cav.) Cuatrec. (studied under the synonym *Banisteriopsis argentea* Spring ex Juss) using standard acid–base extraction of the summary ethanol extract into chloroform, followed by chromatographic methods (Ghosal et al. 1971).

Harmine was also discovered in *Trigonostemon bonianus* Gagnep. (Euphorbiaceae), researched under the synonym *Trigonostemon filipes* Y.T.Chang et S.L.Mo. The plant was air-dried, powdered, and produced a crude extract by extracting three times at room temperature using methanol. Next, the residue of ethyl acetate was subjected to repeated column chromatography over silica gel (Li et al. 2012).

In 1978, harmine was acquired via isolation from a methanol extract of dried aerial parts of *Bassia scoparia* (L.) A.J.Scott (Amaranthaceae), which was studied under the synonym *Kochia scoparia* (L.) Schrad (Drost-Karbowska et al. 1978).

According to Sener and Ergun 1988, harmine was also extracted from an ethanolic extract of the dried climbing plant’s aerial portions *Galium aparine* L. (Rubiaceae), widespread in Anatolia (Sener and Ergun 1988).

Likewise, researchers investigated the bark composition of *Simira williamsii* (Standl.) Steyerf. (studied under the synonym *Sickingia williamsii* Standl.) and *Simira tinctoria* Aubl. (studied under the synonym *Sickingia tinctoria* (Aubl.) Lemée) (Rubiaceae), both of which are typical South American small trees used in Peruvian folk medicine. Harmine was separated from a chloroform/methanol (9:1) extract purified by Sephadex LH-20 column chromatography and RP-HPLC (Capasso et al. 2002). The same group had isolated harmine from *S. williamsii* bark a few years earlier (Aquino et al. 1996).

In addition, a research project in 1971 led to the retrieval of harmine from the extract of *Passiflora incarnata* L. (Passifloraceae) by using Sephadex SE-C 25 column chromatography and TLC (Bennati 1971). Several years earlier, harmine had also been obtained from the leaves and stalks of *P. incarnata*. The extract was prepared by treating the material for 15 h with 25% ammonia, followed by extraction with chloroform, acid–base liquid–liquid extraction, and separation on a cellulose column (Lutomski 1960).

Furthermore, in 2002, harmine was derived from the ethyl acetate portion of a methanolic extract from the whole plant of horseweed, *Erigeron canadensis* L. (Asteraceae). The plant was studied under its synonym *Conyza canadensis* (L.) Cronquist (Mukhtar et al. 2002).

Harmine was also obtained from the dried roots of *Sophora tonkinensis* Gagnep., a herb used in traditional Chinese medicine, through ethanol extraction at room temperature and acid–base liquid–liquid extraction, followed by column chromatography (Wu et al. 2019a).

Additionally, research by Moustafa et al. 2007, led to the uncovering of harmine from *Zygophyllum album* L.f. (Zygophyllaceae), which is locally recognized as a traditional medicine. The aerial parts were air-dried and percolated with ethanol. The acidified extract was then extracted with diethylether and reduced with zinc dust. After alkalization and extraction with chloroform, the resulting alkaloidal fraction was treated by TLC (Moustafa et al. 2007).

Harmine was moreover retrieved from a spiny subshrub of the Solanaceae family, *Lycium europaeum* L., commonly known in Algeria as ‘Awsaj’. This plant is utilized both as food and an herbal remedy. Its roots were extracted with ethanol, followed by an acid–base extraction process to obtain an alkaloidal extract, which was then subjected to silica

gel column chromatography and TLC (Bendjedou et al. 2021).

In 2011, harmine was extracted from the ethyl acetate fraction of the methanolic extract obtained from the marine brown alga, *Malnothamnus afaqhusainii*, using column chromatography (Khan et al. 2011).

To add on, harmine was acquired from *Tribulus terrestris* L. (Zygophyllaceae) growing in Turkey by means of preparative TLC (Tosun et al. 1994). Other researchers have successfully attempted to enhance harmine production in the hairy roots of *T. terrestris* through genetic transformation with *Agrobacterium rhizogenes* strains (Sharifi et al. 2014).

Likewise, harmine was obtained from the aerial parts of the Iranian species *Ducrosia anethifolia* Boiss. (Apiaceae) (Mottaghipisheh et al. 2018). This plant is locally referred to as Moshkbu and Moshgak, and is widely used as both a medicinal plant and a food flavoring agent (Arbabi et al. 2018).

The flowers of *Hosta plantaginea* (Lam.) Asch. (Asparagaceae), a key ingredient in Mongolian medicine, were also found to contain harmine. The air-dried plant material was extracted using 95 and 70% ethanol under reflux. The combined extracts were then partitioned into different solvents, with harmine obtained from the ethyl acetate fraction by applying various chromatographic techniques (Wei and Ma 2020).

Harmine was acquired via isolation from the flowers of *Tabernaemontana divaricata* (L.) R.Br. ex Roem. et Schult. (Apocynaceae) in 2004, marking the first extraction of harmine from this species (Joshi et al. 2004).

Additionally, harmine was retrieved from *Zygophyllum creticum* (L.) Christenh. et Byng (Zygophyllaceae). This plant, however, was studied under the synonym *Fagonia cretica* L (Iyer and Joshi 1975).

In 2020, Zhange et al. 2020b extracted harmine from the stems of *Ohwia caudata* (Thunb.) H. Ohashi., referred to in this study by its synonym, *Desmodium caudatum* (Thunb.) DC. The isolation was achieved through repeated column chromatography on macroporous adsorptive resins, silica gel, and Sephadex LH-20, and by preparative-HPLC (Zhang et al. 2020b).

In a recent study from 2022, harmine was derived via isolation from the root bark of the deciduous tree *Ailanthus altissima* (Mill.) Swingle (Simaroubaceae). The material was refluxed with 85% ethanol and then extracted using an acid–base liquid–liquid procedure. This yielded a concentrated ethyl acetate fraction,

which was further separated using silica gel and Sephadex LH-20 column chromatography. Subsequently, semi-preparative HPLC was employed to isolate harmine, which in this study was incorrectly referenced as 11-methoxy-3-methyl- β -carboline (Shao et al. 2022).

For a convenient overview, all references reporting the isolation of harmine from plant material are alphabetically listed in Table 1.

Interestingly, harmine is also occasionally produced by certain bacterial species. For instance, researchers have discovered harmine production in the *Bacillus* species BT42, which was isolated from the root rhizosphere of *Coffea arabica* L (Kejela et al. 2016). Furthermore, *Bacillus flexus*, obtained from freshwater of a eutrophic lake in Saudi Arabia, was found to produce harmine as a means to inhibit toxic cyanobacteria (Alamri and Mohamed 2013). Additionally, it is known that larvae of Heliconiini butterflies accumulate alkaloids such as harmine by ingesting *Passiflora* leaves (Cavin and Bradley 1988).

Anticancer properties of harmine

Harmine possesses potent cytotoxic and antiproliferative capabilities, according to research conducted over the previous decade. In mice with Lewis Lung Cancer, Sarcoma180, or HepA tumors, harmine demonstrated exceptional anticancer effectiveness, having an excellent inhibition rate of 49.5%. Furthermore, in a mouse Sp2/O tumor model, oral treatment of extracts from *Peganum harmala* at 50 mg/kg for 40 days produced comparable notable outcomes. Harmine and its derivatives also showed impressive in vitro cytotoxicity, with IC₅₀ values ranging from 0.011 to 0.021 μ mol/mL in HepG2 cells. These highlight their potential as potent agents in the battle against cancer. Unfortunately, harmine's substantial neurotoxic impacts in animal models prevented it from being developed clinically. In mice, these consequences included symptoms such as tremors, twitching, leaping, tetanus, and supination. In surviving mice, the tremors lasted around 20 min before gradually diminishing. Notably, all surviving mice healed completely and returned to normalcy by the next day (Chen et al. 2005; Li et al. 2015).

Harmine demonstrates its antiproliferative properties by binding to DNA (Sharma et al. 2016) and

Table 1 Sources of harmine from plants and components utilized

Full botanical name*	English common name	Parts used	References
<i>Alnathus altissima</i> (Mill.) Swingle	Tree of heaven	Root bark	Shao et al. (2022)
<i>Andrographis paniculata</i> (Burm.f.) Wall	Green chirayta	Roots, leaves	Kurzawa et al. (2015)
<i>Banisteriopsis caapi</i> (Spruce ex Griseb.) C. V. Morton	Ayahuasca vine	Stems, branches	Chen and Chen (1939), Rivier and Lindgren (1972), Samoylenko et al. (2010), Santos et al. (2022)
		Leaves, roots	Chen and Chen (1939)
<i>Banisteriopsis muricata</i> (Cav.) Cuatrec	–	Unspecified	Saa Rodriguez (1972)
		Stems, leaves	Ghosal et al. (1971)
<i>Bassia scoparia</i> (L.) A. J. Scott	Mexican fireweed	Aerial parts	Drost-Karbowska et al. (1978)
<i>Ducrosta anethifolia</i> Boiss	–	Aerial parts	Mottaghipisheh et al. (2018)
<i>Erigeron canadensis</i> L	Horseweed	Whole plant	Mukhtar et al. (2002)
<i>Galium aparine</i> L	–	Aerial parts	Sener and Ergun (1988)
<i>Hosta plantaginea</i> (Lam.) Asch	August lily	Flowers	Wei and Ma (2020)
<i>Lycium europaeum</i> L	European tea tree	Roots	Bendjedou et al. (2021)
<i>Ohwia caudata</i> (Thunb.) H. Ohashi	Canadian tick-trefoil	Stems	Zhang et al. (2020b)
<i>Oxalis tuberosa</i> Molina	Wood sorrel	Roots	Bais et al. (2003)
<i>Passiflora incarnata</i> L	Purple passionflower	Unspecified	Bennati (1971), Frye and Haustein (2007)
		Leaves, stalks	Lutonski (1960)
<i>Peganum harmala</i> L	Wild rue	Seeds	Al-Shamma et al. (1981), Astulla et al. (2008), Benarous et al. (2015), Benzekri et al. (2018), Berrougui et al. (2005), Biradar et al. (2013), Cao et al. (2013), Fang et al. (2019), Filali et al. (2015), Gaviraj et al. (1998), Gohar et al. (1994), Chatterjee and Ganguly (1968), Jado et al. (1979), Jiang et al. (2023), Lanchouri et al. (2013), Li et al. (2017), (1989), Ovejero (1947), Shao et al. (2013), Siddiqui and Kemal (1964), Wang et al. (2015a, 2017, 2008), Yang et al. (2015)
		Leaves	Jado et al. (1979)
		Aerial parts	Grabher et al. (2012), Koretskaya (1957), Zhang et al. (2022)
		Stems	Muhtadi et al. (1974)
		Roots	Ayoob et al. (2017)

Table 1 continued

Full botanical name*	English common name	Parts used	References
<i>Peganum multisetum</i> (Maxim.) Bobrov	African rue	Unspecified	Liu (2011)
<i>Peganum nigellastrum</i> Bunge	Bunge	Seeds Aerial parts Aerial parts Seeds Roots Bark Bark Roots Flowers	Duan et al. (1998b) Duan et al. (1998a), Javzan et al. (2017) Ma et al. (2000) Zheng et al. (2009) Babalakova et al. (2011), Ma et al. (2008) Capasso et al. (2002) Aquino et al. (1996), Capasso et al. (2002) Wu et al. (2019a) Joshi et al. (2004)
<i>Simira tinctoria</i> Aubl	–	Roots	Tosun et al. (1994)
<i>Simira williamsii</i> (Standl.) Steyer	–	Unspecified	Li et al. (2012)
<i>Sophora tonkinensis</i> Gagnep	–	Aerial parts	Moustafa et al. (2007)
<i>Tabernaemontana divaricata</i> (L.) R.Br. ex Roem. et Schult	Pinwheel flower	Unspecified	Iyer and Joshi (1975)
<i>Tribulus terrestris</i> L.	Puncture vine	Roots	
<i>Trigonostemon bonianus</i> Gagnep	–	Unspecified	
<i>Zygophyllum album</i> L.f	–	Aerial parts	
<i>Zygophyllum creticum</i> (L.) Christenh. et Byng	Fagonia	Unspecified	

* Accepted names according to World Flora Online database (<http://www.worldfloraonline.org/>) as of 1st August 2023

causing damage to DNA by intercalating into DNA oligonucleotides with a binding preference to GC (Guanine-Cytosine) in comparison with AT (Adenine-Thymine) and, by doing so, impeding DNA topoisomerase I and interfering with DNA synthesis and replication (Nafisi et al. 2010; Shu et al. 2019; Song et al. 2004). Harmine can cause significant structural DNA damage by binding and interacting with DNA. The synthesis of the harmine-DNA combination is exothermic and spontaneous, involving interactions between the harmine and the DNA via H-bonding, van der Waal and hydrophobic interactions (Sharma et al. 2016).

It has been established that the compounds of β -carboline and harmine have anti-angiogenic properties. They can suppress the production of pro-angiogenic factors and restrict the growth of vascular endothelial cells, which prevents the development of new blood vessels that are essential for tumor growth and metastasis (Tshikhudo et al. 2024). VEGF, or vascular endothelial growth factor, is necessary for angiogenesis. Harmine inhibits the NF- κ B signaling system, which suppresses tumor angiogenesis by decreasing the synthesis of proangiogenic molecules such as VEGF, NO, and other factors such as interleukin-2, matrix metalloproteinases (MMPs), cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (Hai-Rong et al. 2019; Hamsa and Kuttan 2010).

Under normal biological conditions, the body naturally removes aged cells through apoptosis, also known as programmed cell death. On the other hand, aberrant signaling pathways in tumors cause unchecked growth of cells that ultimately compromises the tumor's ability to survive or cause recurrence of cancer (Mohammad et al. 2015). In human gastric carcinoma cells like BGC-823, (Zhang et al. 2016a), SGC-7901 (Li et al. 2017; Zhang et al. 2016a) and MGC-803 (Zhang et al. 2016a), harmine triggered apoptosis and diminished proliferation. Activating Myt1, phosphorylating and deactivating Cdk2, and upregulating p21 were the methods by which it caused cell cycle arrest in MGC-803 cell lines during the G2 phase. After 24 h of treatment with harmine (0, 5, 10, and 20 μ M), various apoptotic proteins (such as caspase-9, caspase-8, caspase-3, and its substrate, PARP (Poly (ADP-ribose) polymerase)) were activated by cleavage. The intact proteins disappeared at higher harmine concentrations, and in a concentration-

dependent manner, bands of proteolytic cleavage appeared (Li et al. 2017; Zhang et al. 2016a).

Furthermore, harmine inhibited the Erk/Bad pathway and activated the caspase-8/Bid pathway to initiate the mitochondrial-related process of apoptosis (Zhang et al. 2016a). Harmine also demonstrated dose-dependent Bcl2 downregulation, which inhibited the proliferation of thyroid TPC-1 cells using harmine concentrations of, 8, and 16 μ g/mL and exposing them for 6 h. The Western blot technique was used to assess the expression of proteins linked to apoptosis in order to look into potential mechanisms for apoptotic induction following harmine exposure. The administration of harmine resulted in a dose-dependent induction of Bax expression and the degradation of pre-existing Bcl-2, which led to a noteworthy reduction in the Bcl-2/Bax ratio, signifying the advancement of apoptosis (Ruan et al. 2017).

Moreover, harmine reduced Bcl-2 expression in melanoma B16F-10 cells and promoted apoptosis by triggering Bax, caspase-3/-8/-9, and Bid. Apoptosis at 1 and 2 μ g/mL of harmine was also significantly increased. Nuclear staining revealed morphological alterations indicative of apoptosis, including membrane blebbing, chromatin condensation, DNA breakage, and the formation of apoptotic bodies (Hamsa and Kuttan 2011).

Lastly, harmine has been demonstrated to be effective against hepatic HepG2, Bel-7402 and SMMC7221 cells due to the apoptotic mechanisms it produces. It does this by lowering the expression of Bcl-2 and Mcl-1 and stimulating cellular apoptosis through the induction of Bax, Fas, and caspase 3/– 9. Fluorescence microscopy was used to evaluate apoptotic nuclear morphology following Hoechst 33,258 staining. HepG2 cells started to demonstrate apoptotic signs such as shrinkage of the cells, nuclear condensation, and cell fragmentation after 48 h of treatment with 5 μ g/mL harmine. In addition, HepG2 cells were treated with 5, 10, and 20 μ g/mL harmine for 48 h, and flow cytometry using propidium iodide (PI) for DNA staining revealed that this increased the number of cells in the S and G2/M phases (Cao et al. 2011).

Protein kinases are important for several biological activities. Cyclin-dependent kinases (Cdks) are crucial elements of the molecular machinery involved in the cell cycle. An essential modulator of the replication of DNA and the progression of the S phase is Cdk2. Harmine inhibited Cdk1/cyclin B, Cdk2/cyclin A, and

Cdk5/p25, with IC_{50} values of 17, 33, and 20 μ M, in that order. Cdk activity is inhibited when harmine binds to their ATP-Mg²⁺-binding pocket (Song et al. 2004). Overexpression of the dual-specificity tyrosine-phosphorylated and regulated kinase 1A (DYRK1A) has been linked to cancer and uncontrolled cell proliferation. Harmine is a potent inhibitor of the DYRK1A protein kinase. Harmine-induced DYRK1A inhibition resulted in apoptosis and caspase-9 activation in human oligodendroglioma (Hs683) cancer cells (Atteya et al. 2017; Frédérick et al. 2012).

Overexpression or deletion of haspin, a nuclear protein kinase unique to haploid germ cells causes improper mitosis, and inhibiting haspin has significant anticancer effects (Amoussou et al. 2018). With an IC_{50} of 0.59 μ M, harmine is a moderately effective haspin inhibitor (Cuny et al. 2012).

Among other important kinases, GSK-3 is a serine/threonine kinase that has been recognized as a regulator of glycogen metabolism. It regulates a wide range of known substrates and is essential for many cellular processes, such as the regulation of cell cycles, proliferation, differentiation, and gene expression (Hamann et al. 2007; Maqbool et al. 2016). This essential kinase engages in interactions with numerous signaling pathways, including Ras/Raf/MEK/Erk, PI3K/PTEN/Akt/mTORC1, Wnt/ β -catenin, Notch, Hedgehog, and others. Numerous human illnesses, including cancer, bipolar depression, Parkinson's, Alzheimer's, and non-insulin-dependent diabetic mellitus, have been linked to aberrant GSK-3 activity. GSK-3 may therefore be a crucial therapeutic target for treating these and other illnesses. Moreover, GSK-3 has been connected to malignancies that resist targeted therapy, radiation, and chemotherapy. GSK-3 targeting could help treat malignancies that are resistant to radiation, some chemotherapeutic medications, and small molecule inhibitors. Some GSK-3 inhibitors have been included in clinical trials I/II (McCubrey et al. 2014). Interestingly, potent GSK-3 inhibitors were found among β -carboline alkaloids (for example, manzamine present in several marine sponge species and others (Dai et al. 2018).

From the viewpoint of structure–activity relationship (SAR), a series of harmine derivatives was prepared by incorporation of various substituents at positions-1, 2, 6, 7 and 9. SAR studies showed that the N9-position participates in an important role in regulating anticancer activity. To date, 26 N9-

substituted harmine derivatives have been prepared. Most of these are represented by amines; 4 amides, and 2 sulfonamides have also been synthesized. Antiproliferative and viability activity of these harmine derivatives was tested on 4 tumor cell lines (MCF-7, SGC7901, SMMC-7721, and A-549). Du et al. (Du et al. 2016) reported the SAR for N9-substituted harmine derivatives: (1) N9-bromoalkyl harmine derivatives are more potent than N9-chloroalkyl and N9-alkyl harmine derivatives; (2) inhibitory activity increases with increasing chain length for N9-bromoalkyl analogs; (3) in the series of N9-aryl harmine derivatives, their activity decreases in the order N9-benzensulfonyl, N9-benzoyl, and N9-benzyl analogs. Harmaline and tetrahydroharmine, alkaloids found in *Peganum harmala* seeds, represent naturally prepared analogs of harmine. Harmaline differs from harmine by the absence of a single double bond in ring C. Tetrahydroharmine is saturated with four additional hydrogen bonds compared to harmine. Harmaline and tetrahydroharmine possess promising anticancer activities (Simão et al. 2020; Tarpley et al. 2021; Wang et al. 2015b). Interestingly, no N9-substituted harmaline and tetrahydroharmine derivatives have been published so far.

Furthermore, when harmine is coupled with chemotherapy medications, it has a synergistic anticancer impact. Harmine has been proposed as a possible treatment candidate for a number of malignancies when combined with paclitaxel. The combined administration of harmine and paclitaxel has a synergistic impact on the downregulation of matrix metalloproteinase 9 (MMP-9) and cyclooxygenase 2 (COX-2) in the gastric cancer cell lines SGC-7901 and MKN-45, resulting in a reduction of proliferation and activation of apoptosis (Yu et al. 2016). Cells treated with 2 ng/mL paclitaxel, 4 μ g/mL harmine or a combination of these two drugs for 48 h were examined using Western blot analysis. The combination application of harmine and paclitaxel resulted in a significant reduction in COX-2 expression when compared to the effects of each medication alone, according to the results. COX-2 is frequently expressed in stomach cancer and has been linked to metastasis and tumor invasiveness (Sun et al. 2015). Previous research has shown that selective COX-2 inhibitors or small interfering RNA (siRNA) can reduce COX-2 activity and cause apoptosis in human gastric cancer cells. It has been noted that harmine

reduced the expression of COX-2, which prevented stomach cancer cells from migrating and invading (Chan et al. 2007). The anticancer potential of harmine stems from the molecular mechanisms by which this β carboline amine alkaloid exerts inhibitory effects in various malignancies, which are discussed below.

Breast cancer

Breast cancer is among the most frequent cancers in women, contributing to over one-tenth of the new cases of cancer each year. It is the second biggest contributor to cancer-related deaths in women worldwide (Alkabban and Ferguson 2022). TAZ, a transcriptional coactivator with a PDZ-binding motif, is involved in breast cancer progression and development. TAZ promotes growth, migration, and metastasis in breast cancer. Harmine decreased the growth of cells and migration, as well as the expression of TAZ, phosphorylated Erk (p-Erk) at Thr 202 and Tyr 204, phosphorylated Akt (p-Akt) at Ser 473 and Bcl-2, but increased expression of Bax (Ding et al. 2019). Harmine inhibited MCF-7 cells (epithelial cells from breast adenocarcinoma) from proliferating by suppressing telomerase activity via the p53/p21 pathway. Telomerase activity in MCF-7 cells was measured via the telomerase repeated amplification procedure (TRAP). After the cells were exposed to 20 μ M harmine for 96 h, a reduction in telomerase activity by 81.9% was found (Zhao and Wink 2013).

Harmine can also stop the migration and invasion of breast cancer cells, which are the initial steps toward metastasis. By inducing dose dependent Twist1 degradation mediated by proteasomes, this is accomplished. Twist1 has been found to positively regulate the metastasis of breast cancer and is overexpressed in several cancers. It induces epithelial-to-mesenchymal transition (EMT) and cell invasion by activating numerous target genes, including Snail, Bmi1, and ZEB2, which accelerate cellular de-differentiation and cell motility. During EMT, cells transition from an epithelial to a mesenchymal-like phenotype. When mesenchymal markers like vimentin and N-cadherin are expressed and epithelial markers like E-cadherin are lost, cell–cell adhesion breaks down, signaling the start of epithelial-mesenchymal transition (EMT).

Because EMT promotes invasion and intravasation into the bloodstream and activates proteases involved in the degradation of extracellular matrix, it seems to be connected to the development of cancer. BT549 Twist + cells were subjected to three different treatments: dimethyl sulfoxide (DMSO) as a solvent control, harmine treatment at final concentrations of 5, 10, and 20 μ M, or no treatment at all. After collecting, lysing, and Western blotting the lysates to determine the amount of Twist1, it was discovered that Twist1 was degraded harmine dose-dependently (Nafie et al. 2021).

To boost harmine's water solubility and bioavailability, harmine hydrochloride (HMH) was prepared. The reaction between harmine and hydrochloric acid to form harmine hydrochloride is a type of acid–base reaction, specifically a neutralization reaction. In this reaction, the acidic hydrochloric acid reacts with the basic harmine to form a salt (harmine hydrochloride) and water. In the breast cancer cells, MCF-7, treatment with it inhibited cell proliferation, migration, invasion, and colony formation. It also raised FOXO3a expression and decreased the phosphorylation of PI3K, Akt, and mTOR. A dose-dependent increase in p38 phosphorylation was also seen in MCF-7 cells after HMH administration. G2/M cell cycle arrest was triggered by activated FOXO3a through upregulating the levels of expression of p21, p53, and its downstream proteins, such as p-Cdk2, Cdk2, p-Cdc25 phosphatase, and cyclin B1. HMH was added to MCF-7 cells at different concentrations (0–1000 μ M) for 24–72 h, and the effect of the treatment on cell proliferation was measured to see if HMH could restrict the growth of cells from human breast cancer. The IC_{50} values in MCF-7 cells after 24 h, 48 h, and 72 h of HMH treatment were 100.6, 52.4, and 18.7 μ M, respectively. Western blot analysis was performed on breast cancer cells treated with 5, 10, and 20 μ M HMH for 48 h to assess the suppressive effects on protein expression. HMH reduced the expression of PI3K, p-PI3K, Akt and p-Akt in MCF-7 cells in a dose-dependent manner, while mTOR and p-mTOR expression was reduced by 20 μ M HMH compared to the control. HMH substantially suppressed Akt and p-Akt activation in MCF-7 cells, according to Western blot analysis (Ock and Kim 2021).

Lung cancer

Lung cancer is the most frequently diagnosed cancer worldwide and the primary cause of cancer-related deaths, with an estimated two million new cases and a total of 1.76 million deaths annually (Thai et al. 2021). The two most common kinds of lung cancer are non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLCs account for approximately 80% of newly diagnosed lung cancer cases each year (Shen et al. 2014).

Harmine demonstrated cytostatic properties in NSCLC cells, with IC_{50} values ranging from 10.11 to 32.74 μ M, while having no effect on MRC-5 cells. Harmine also efficiently triggered cell cycle arrest and death in NSCLC cells in the G1/S phase. A549 cells were treated with various concentrations of harmine (0, 5, 10, and 20 μ M) for 24 h, and cell cycle distribution analysis was performed using flow cytometry, which revealed an increase in the G1 phase population with harmine-treated cells in a dose-dependent manner. Along with the cell cycle analysis, the TUNEL assay staining with flow cytometry-based quantification revealed that treatment with harmine at a final concentration of 5, 10 and 20 μ M significantly induced DNA fragmentation of A549 lung cancer cells, implying that the treatment caused G1/S phase arrest and apoptosis in A549 cells (Shen et al. 2018). Harmine also reduced the expression of Mcl-1 and made the non-small cell lung cancer cells more sensitive to inhibitors of Bcl-2 because, in NSCLC, the expression of Mcl-1 results in acquired resistance to the inhibitors of Bcl-2. Mcl-1 is an anti-apoptotic protein which is essential in the development of resistance to anti-cancer drugs. The combination of harmine with a Bcl-2 antagonist demonstrated synergistic anti-proliferative effects in primary NSCLC cell lines. Primary NSCLC cells were treated for 72 h with harmine and/or Bcl-2 inhibitor with concentrations ranging from 0–30 μ M, and NSCLC cell proliferation was assessed using a sulforhodamine B (SRB) assay. The mean combination index (CI) value was less than 0.9. The degree of drug interaction is determined using CI and synergism should be less than 1 (Li et al. 2020).

Twist1, a transcription factor involved in epithelial-mesenchymal transition (EMT), has been identified as a cause of resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non-small cell lung cancer cells and is important for its

oncogene-driven carcinogenesis. Harmine was able to overcome this resistance and showed significant anticancer activity in oncogene-driven NSCLC (Yochum et al. 2017, 2019).

Furthermore, harmine efficiently led to a cell cycle arrest and death in the G1/S in NSCLC cells by stimulating the reversion-inducing cysteine-rich protein with Kazal motif expression as well as the signaling pathway cascade from it, resulting in MMP-9 and E-cadherin downregulation. The protein expression of Akt, STAT3, Erk, EMT, and MMP-9 on A549 cells was evaluated by Western blotting after harmine treatment with doses of 0 (served as negative control), 10, and 20 μ M exhibiting a substantial reduction in STAT3, Akt, Erk, and MMP-9 expression (Shen et al. 2018).

Gastric cancer

Worldwide, gastric cancer is the fifth most common cancer and the third leading cause of cancer death. Infection with *Helicobacter pylori*, age, a high salt intake, and a diet low in fruits and vegetables are all risk factors for the condition (Smyth et al. 2020).

Harmine triggered apoptosis and reduced the growth, migration, and metastasis of BGC-823 and SGC-7901 human gastric cancer cells. COX-2 is essential in the development and progression of gastric cancer, and a study carried out by Zhang et al. 2014 showed that harmine significantly reduced COX-2 expression in SGC-7901 and BGC-823 gastric cancer cell lines. To investigate the effects of harmine on COX-2 expression, gastric cancer cell lines were exposed to harmine (0, 4, 8, 16 μ g/mL), and Western blot analysis revealed that harmine suppressed COX-2 expression in BGC-823 and SGC-7901 cells in a dose-dependent manner (Zhang et al. 2014).

The western blot results showed that HMH down-regulated Bcl-2, Bcl-xL, and Mcl-1 and upregulated Bax and Bok in human gastric carcinoma MGC-803 cell line. The expression of the BH3-only family member protein Bad increased, while phosphorylated Bad (Ser112) and full-length Bid were concurrently reduced. Exposure to harmine for 24 h resulted in the activation of several apoptotic proteins, including caspase-9, caspase-8, caspase-3, and its substrate PARP, through cleavage. The Zhang and co-workers found that of p-Erk was reduced and p-JNK was unchanged in human gastric cancer cells, implying that

harmine stimulated apoptosis via the mitochondria-related pathway by inhibiting the Erk/Bad signaling pathway and activating the caspase-8/Bid pathway. It also caused a G2 phase cell cycle arrest in both SMMC-7721 and MGC-803 cells by phosphorylating and deactivating Cdk2, activating Myt1 and upregulating p21. Harmine administration resulted in a large accumulation in the G2/M phase in a dose-dependent manner using the following doses for 24 h: 0, 5, 10, and 20 μM , accompanied by a considerable decrease in the G1 phase population (Zhang et al. 2016a).

Moreover, when coupled with certain chemotherapy treatments, harmine has synergistic anti-gastric cancer benefits. The combination of paclitaxel and harmine inhibited proliferation and triggered the activation of apoptosis in SGC-7901 and MKN-45 cells. MTT ((3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium) reduction assays were used to examine the metabolic activity of proliferating cells. When given separately, the results showed that paclitaxel and harmine suppressed cell growth in a dose-dependent manner. Furthermore, the inhibitory effects of paclitaxel (0.25, 0.5, 0.75, 1 and 2 ng/mL) and harmine (0.5, 1, 1.5, 2, and 4 $\mu\text{g/mL}$) combination therapy on cell proliferation were greatly improved and exhibited notable inhibition at lower doses in SGC-7901 and MKN-45 cells (Sun et al. 2015).

Colon cancer

Colorectal cancer is the third most common cancer diagnosis and the second most lethal tumor in both men and women. Its risk factors are strongly associated with both environmental and genetic factors. Colon cancer is caused by inherited disorders such as hereditary non-polyposis colorectal cancer (Lynch syndrome) and familial adenomatous polyposis (FAP) (10% of the time) and familial clustering (20% of the time), but the occurrence may be sporadic for 70% of the time (Lotfollahzadeh et al. 2022b).

Harmine inhibited the Erk and Akt signaling pathways, resulting in cell cycle arrest and apoptosis via the mitochondrial pathway in SW620 colorectal cancer cells by stimulation of caspase-9, caspase-3, Bax upregulation and downregulation of Bcl-2, Mcl-1, and Bcl-xL. Fluorescence microscopy was used to

evaluate apoptotic nuclear morphology with Hoechst 33,258 staining. The SW620 cells began to display apoptotic features such as cell shrinkage, nuclear condensation, and fragmentation after 48 h of treatment with 5.00 $\mu\text{g/mL}$ harmine. The Akt signaling pathway was investigated to determine the mechanism of cellular apoptosis produced by harmine in SW620 cells. SW620 cells were treated for 48 h with various doses of harmine (0, 0.625, 1.25, 2.5, and 5 $\mu\text{g/mL}$). Western blot analysis was used to examine the levels of phosphorylation of Erk, Akt, and its downstream targets FoxO3a and GSK-3 β . Increased harmine concentrations reduced the phosphorylation of Ser473-Akt and Thr308-Akt in a dose-dependent manner without changing the overall quantity of Akt (Liu et al. 2016).

In a different investigation, through the suppression of the protein kinase DYRK1A, harmine demonstrated anti-proliferative effects against colon (Caco2) cancer cells (Bruehl et al. 2014). Harmine treatment resulted in increased expression of Bax, caspase-3, and PARP cleavage, as well as reduced activity of Bcl-2, CDK5/p25, and GSK3 β / against colorectal RKO and DLD1 cells (Zhang et al. 2016b).

Liver cancer

Hepatocellular carcinoma is one of the most common forms of primary liver disease. In most situations, it is usually caused by persistent hepatitis B and C viral infections. It is more likely in the elderly population, which may have chronic liver disease. Ethanol consumption and metabolic syndrome have also been associated with the development of liver cancer, with continuous liver damage leading to steatosis, steatohepatitis, cirrhosis, and, eventually, hepatocellular carcinoma (Lotfollahzadeh et al. 2022a).

Harmine activated caspase-3 and caspase-9, as well as downregulating Bcl-2 and Mcl-1 expression, causing apoptosis via the mitochondrial signaling pathway in HepG2 cells. Fluorescence microscopy was used to evaluate apoptotic nuclear morphology with Hoechst 33,258 staining, which revealed HepG2 cells showing apoptotic features such as cell shrinkage, nuclear condensation, and fragmentation after 48 h of treatment with 5 $\mu\text{g/mL}$ of harmine. It activated Bcl-2 family members, caspase-3, and caspase-9 in HepG2

cells after 48 h of treatment with 0, 1.25, 2.5, and 5 $\mu\text{g/mL}$ of harmine. Immunoblotting was used to measure the impact of harmine on protein expression levels (Cao et al. 2011).

HMH also inhibited SMMC-7721 human hepatocarcinoma cells. It substantially suppressed SMMC-7721 cell proliferation in a dose-dependent manner after 14 days of treatment with 0, 1, 2, 4, 8, and 16 μM concentrations of harmine, according to the colony formation assay. The experiments aimed at exploring pro-apoptotic markers indicated that the apoptosis rates of SMMC-7721 cells increased with HMH treatment in a dose-dependent manner, as observed through flow cytometry Annexin V and propidium iodide analysis. Furthermore, Western blot results illustrated the cleavage of caspase-3 and PARP upon HMH treatment, confirming the induction of cell apoptosis. HMH exposure influenced mitogen-activated protein kinases (MAPK) signaling, leading to an increase in p-JNK (Thr183/Tyr185) expression and a reduction in p-Erk (Thr202/Tyr204) in SMMC-7721 liver carcinoma cells (Zhang et al. 2016a).

Polycyclic aromatic hydrocarbons are metabolized by CYP1A1 into intermediates which are reactive and capable of creating DNA mutagenesis, and the development of cancer. As a result, CYP1A1 is regarded as a valuable biomarker for exposure to some carcinogens. By decreasing aryl hydrocarbon receptor-dependent luciferase activity and triggering the receptor for aryl hydrocarbon, harmine efficiently reduced dioxin-mediated and 2,3,7,8-tetrachlorodibenzo-p-dioxin mediated CYP1A1 enzyme activity in hepatoma cells (El Gendy et al. 2012; El Gendy and El-Kadi 2013).

To prevent either apoptosis or cell cycle arrest, rapidly developing malignant cells must activate DNA double strand break (DSB) repair to repair replication stress induced DSBs. As a result, finding medications to suppress homologous recombination (HR) and nonhomologous end joining (NHEJ), two critical DSB repair pathways, has considerable potential for cancer therapy. Harmine inhibited Rad51 recruitment in Hep3B and HuH7 hepatoma cell lines, which inhibited homologous recombination and increased DNA double-strand breaks, as well as severe S or G2/M phase arrest. After being pretreated with 40 μM harmine for 2 h, Hep3B cells were exposed to an 8 Gy X-ray. The formation of Rad51 foci was examined by immunofluorescence 6 h after irradiation, leading to the finding that harmine suppresses

the development of Rad51 foci following DNA damage (Zhang et al. 2015).

Glioblastoma

The most prevalent cancerous tumors of the central nervous system are glioblastomas. Despite new molecular discoveries and therapeutic breakthroughs, the prognosis for glioblastoma patients remains dismal, with a median survival time of 12–15 months after surgery (Wen and Kesari 2008). Glioblastoma has this poor prognosis because of its characteristics, which include fast recurrence and rapid growth. Furthermore, the blood–brain barrier prevents the administration of some anticancer medications into tumor areas, limiting the chemical compounds available for glioblastoma treatment (Doolittle et al. 2000).

The treatment of many cancers and brain disorders has been researched for harmine hydrochloride (HMH). HMH inhibited Akt phosphorylation, created apoptosis, and decreased cell viability in glioblastoma cell lines, according to study done by Lui et al. 2013. By using concentrations of 6.25, 12.5, 25, 50, and 100 μM for either 24 or 48 h, HMH substantially reduced the viability of glioma cell lines C6, U87, and U373 using the MTT assay. This effect was dose- and time-dependent. HMH had IC_{50} values of 22.9 μM (C6), 26.2 μM (U87), and 27.2 μM (U373) at 48 h, and 37.5 μM (C6), 47.3 μM (U87), and 44.7 μM (U373) at 24 h. HMH also reduced the tumorigenicity of glioblastoma stem-like cells (GSLCs) in an in vivo test. Treatment of glioblastoma cells with HMH significantly upregulated the mRNA expression of Bax while downregulating the mRNA expression levels of Bcl-2 and Bcl-xL, inducing an imbalance in apoptosis-related molecules. Furthermore, the cleavage of caspase-3 was notably activated by HMH in a dose- and time-dependent manner. As a result, it was concluded that HMH has significant anticancer effects in glioblastoma cells, which are mediated at least in part by Akt phosphorylation inhibition, and that HMH administration might be a novel strategy for glioblastoma therapy (Liu et al. 2013). Later study of Zhu and co-workers, focused on investigating the anti-tumor effect of harmine on glioblastoma, revealed that harmine inhibited the proliferation and migration of glioblastoma by downregulating the Fak/Akt pathway. Mechanistically, harmine downregulated the phosphorylation of the Fak/Akt pathway, resulting in decreased cell viability of

U251-MG and U373-MG glioblastoma cells. Additionally, harmine suppressed the migration of U251-MG cells by reducing the expression of MMP2, MMP9, and VEGF. Furthermore, in orthotopic xenograft models, harmine treatment significantly inhibited the growth of glioblastoma *in vivo* (Zhu et al. 2021).

Neuroblastoma

Neuroblastoma (NB) is a pediatric cancer that arises from the sympathetic nervous system as it develops and results in aggressive tumor growth in either the sympathetic ganglia or the adrenal glands and sometimes even in both (Becker 2012). Despite rigorous, multimodal therapy, patients frequently come with advanced illnesses and the survival odds are less than 50% (Matthay et al. 2016).

According to a study by Uhl et al. 2018, harmine triggers caspase-3/7 and caspase-9 to become active in NB cells. NB cell lines (KELLY, SKNFI, SKNBE and SKNAS) were exposed to harmine (0, 50, and 100 μM) for 24 h, and the Caspase-Glo Assay Systems were used to detect caspase activity. After 72 h of treatment, the IC_{50} values for harmine for SKNBE, KELLY, and SKNFI were 169.6, 170.8, and 791.7 μM , respectively. As early as 24 h after treatment, those NB cell lines exposed to 100 μM of harmine showed activation of caspase-3/7 and caspase-9, as well as caspase-mediated PARP cleavage, and cells stained with Annexin V strongly indicating induction of apoptosis. Harmine can also inhibit the actions of dual-specificity tyrosine phosphorylation-regulated kinase (DYRK) family proteins, as well as mitogen-activated protein kinases (MAPK), which are kinases that stimulate proliferation while inhibiting apoptosis (Uhl et al. 2018).

Pancreatic cancer

Pancreatic cancer is one of the deadliest diseases and one of the main causes of cancer-related deaths in the United States, with a five-year survival rate of roughly 10%. Smoking, type 2 diabetes, obesity, and a family history of the disease are risk factors for pancreatic cancer. When the cancer is still localized, patients generally present with advanced illness due to a lack of symptoms or unclear symptoms. The most effective way for identifying a pancreatic tumor and determining if it can be surgically resected is often high-quality computed tomography with intravenous contrast

employing a dual-phase pancreatic protocol (Mizrahi et al. 2020). Pancreatic carcinoma is expected to be the second-highest cause of cancer-related mortality by 2030 (Rahib et al. 2014).

Harmine decreased the growth of the pancreatic cancer cells: PANC-1, SW-1990, CFPAC-1, and BxPC-3. These cells were treated with concentrations of harmine at 0, 10, 20, 30, and 40 μM for 24, 48, and 72 h, and the sulforhodamine B (SRB) assay was used to evaluate cell proliferation. Harmine greatly decreased the proliferation of pancreatic cancer cells in a dose- and time-dependent manner. Furthermore, harmine caused cell cycle arrest in BxPC-3 and PANC-1 cells in the G2/M phase of the cell cycle. Interestingly, this cell cycle arrest was followed by cyclin B1 and p21 activation, accompanied by c-Myc inhibition in the cancer cells. Aberrant activation of the PI3K/Akt/mTOR pathway plays a significant role in carcinogenesis, as this pathway is crucial for the motility, growth, survival, and metabolism of cancer cells. Experiments on pancreatic cells indicated that harmine dose-dependently (0–30 μM) suppressed the Akt/mTOR pathway in PANC-1 and BxPC-3 cells (Wu et al. 2019b).

Moreover, harmine and gemcitabine together appear to be a promising therapeutic option for pancreatic cancer patients. Typically, pancreatic cancer is discovered at a late stage, and gemcitabine-based treatment has been used as the initial line of treatment for the disease's metastatic form (Fuchs et al. 2015). According to Wu et al. 2019a, b, harmine and gemcitabine synergistically inhibited pancreatic cancer cell growth with mean combination index (CI) values less than 0.9. Pancreatic cancer cells were cultured with harmine and/or gemcitabine at various doses for 72 h, and the cytotoxicity of harmine combined with gemcitabine was determined using the SRB assay (Wu et al. 2019a, b).

Thyroid cancer

Thyroid cancer is a form of cancer that develops in the thyroid parenchymal cells. Its global prevalence is progressively growing, although fatality rates have remained steady in recent years. Thyroid cancer has a wide range of clinical characteristics, from indolent, slowly growing tumors to extremely aggressive tumors with significant fatality rates (Lee et al. 2023).

In vitro treatment with harmine (2, 4, 8, 16, 32, and 64 $\mu\text{g/mL}$) on TPC-1 cells for 24, 36, and 48 h

Table 2 The half maximal inhibitory concentration (IC₅₀) of harmine on cancerous cell lines after 24 and 48 h of exposure

Tumor cell line		Anticancer activity (IC ₅₀ [μM])		References
		24 h	48 h	
Breast cancer	MCF-7	100.6	52.4	Ock and Kim (2021)
	MDA-MB-231	91.9	17.7	
Gastric cancer	SGC-7901	40.94 ± 5.65	12.29 ± 2.49	Li et al. (2017)
	MGC-803	58.84 ± 11.34	19.97 ± 3.98	
Liver cancer	Hep3B	27.09 ± 5.11	15.74 ± 0.95	Zhang et al. (2015)
	HuH7	43.82 ± 2.93	19.50 ± 0.70	
Glioblastoma	U373	44.7	27.2	Liu et al. (2013)
	C6	37.5	22.9	
	U87	47.3	26.2	
Neuroblastoma	KELLY	3395 ± 7.90	238.7 ± 0.13	Uhl et al. (2018)
	SKNBE	558.7 ± 1.10	224.8 ± 0.16	
Lung cancer	A549	–	10.11	Shen et al. (2018)
	H460	–	19.45	
	PC9	–	32.74	
Pancreatic cancer	PANC-1	15.58 ± 1.04	9.29 ± 0.42	Wu et al. (2019b)
	BxPC-3	41.95 ± 3.39	19.2 ± 0.54	
	CFPAC-1	36.00 ± 0.96	12.35 ± 1.39	
	SW1990	31.78 ± 2.03	11.53 ± 0.47	

*IC₅₀—the concentration at which 50% of viable cells are inhibited

decreased TPC-1 cell proliferation in a time- and dose-dependent manner. At 24, 36, and 48 h, the IC₅₀ values of harmine against TPC-1 cells were 16.57 ± 1.4, 9.48 ± 1.1, and 5.51 ± 0.7 μg/mL, respectively. Furthermore, using western blotting to evaluate the expression of apoptosis-related proteins, harmine treatment dose-dependently induced the production of Bax while degrading the existing Bcl-2, resulting in a substantial reduction in the Bcl-2/Bax ratio, indicating the progression of apoptosis (Ruan et al. 2017).

Recent study of Baldini et al. have demonstrated that harmine can exert multiple anti-cancer effects against anaplastic thyroid carcinoma cell lines BHT-101 and CAL-62. It has been demonstrated that harmine reverses the epithelial-mesenchymal transition (EMT) by upregulating E-cadherin and downregulating fibronectin expression. This effect is primarily attributed to the reduction in Twist1 expression. Additionally, harmine inhibits the proliferation, motility, and anchorage-independent growth of anaplastic thyroid carcinoma cells. Moreover, harmine applied at 20 μM for 24 h or 48 h led to a significant reduction in the activation of the PI3K/Akt signaling pathway, while the activation of the MAPK pathway remained unaffected (Baldini et al. 2024).

All the discussed anticancer activities against various tumor cell lines of harmine and anticancer mechanisms are summarized in the following tables (Tables 2 and 3). The mode of action of harmine in various cancer histotypes is illustrated in Fig. 2.

Harmine derivatives exhibiting significant antitumor potential

The structure of harmine has been intentionally modified to produce derivatives which possess either specific properties or to enhance certain effects (Zhang et al. 2020a). These modifications were aimed at optimizing the therapeutic potential of harmine. By introducing specific substitutions or alterations, scientists have sought to enhance the anticancer activity, selectivity, and other important pharmacokinetic properties of harmine. Structure–activity relationship (SAR) studies aim to elucidate the relationship between the structure of a compound and its biological activity. Researchers have systematically investigated how modifications to the structure of harmine impact its potency, selectivity, and other pharmacological

Table 3 Summary of anticancer mechanisms of harmine on the various cancer types

Type of Cancer	Mechanism	Effects and targets	References
Breast	Cytostatic	↓ telomerase activity	Zhao and Wink (2013)
	Cell cycle arrest	G2/M phase cell arrest	Ock and Kim (2021)
		↑ p21	
		↑ p53	
Lung	Apoptosis	↑ Cyclin B1/Cdk 2	Nafie et al. (2021)
		PI3K/Akt/TOR pathway inhibition	
		↑ FOXO3a	
	Decreased cell invasion	↓ EMT markers expression	Li et al. (2020)
		↓ Twist1	
		G1 phase arrest	
Gastric	Cell cycle arrest	↓ Mcl-1	Shen et al. (2018)
		↓ Bcl-2 expression	
		↓ STAT3	
		↓ Akt	
	Apoptosis	↓ Erk	Yochum et al. (2017)
		↓ MMP-9	
		↓ Twist1	
		G2/M phase cell arrest	
		↑ p21	
		Activate Myt1	
Colon	Apoptosis	Deactivate Cdk2	Zhang et al. (2014)
		↓ Bcl-2	
		↓ Bcl-xL	
		↓ Mcl-1	
		↑ Bax	
		↑ Bok	
		↑ caspase-9, -8, -3	
		↑ Cleaved-PARP	
		↓ Erk	
		↓ COX-2 expression	
		Inhibit Erk and Akt pathway	
		Activate caspase-3 and caspase-9	
		↓ Bcl-xL	
		↓ Mcl	
		↓ Bcl-2	Zhang et al. (2016b)
		↑ Cleaved-PARP	
		↑ Bax expression	
		Suppress DYRK1A	
		↓ CDK5/p25	Zhang et al. (2016b)
		↓ GSK3β	

Table 3 continued

Type of Cancer	Mechanism	Effects and targets	References
Liver	Cell cycle arrest	G2/M phase cell arrest Inhibit Rad51	Zhang et al. (2015)
	Apoptosis	Activate caspase-3 and caspase-9 ↓ Bcl-2 expression ↓ Mcl-1 expression ↑ JNK ↓ Erk ↑ Cleaved-PARP	Cao et al. (2011)
Glioblastoma	Apoptosis	Inhibit Akt phosphorylation ↑ Bax ↓ Bcl-2 and Bcl-xl ↓ Fak and Akt	Liu et al. (2013)
	Decreased cell invasion	↓MMP2, MMP9 and VEGF	Zhu et al. (2021)
Neuroblastoma	Apoptosis	Activate caspase -3/7 and caspase 9 ↑ Cleaved-PARP Inhibit DYRK	Zhu et al. (2021)
			Uhl et al. (2018)
Pancreatic	Cell cycle arrest	G2/M phase cell arrest ↑ p21 Cyclin B1 activation c-Myc inhibition ↓ Akt and mTOR	Wu et al. (2019b)
	Apoptosis	↑ Bax ↓ Bcl-2 ↓ PI3K and Akt	Ruan et al. (2017)
Thyroid	Decreased cell invasion	↑ E-cadherin ↓ fibronectin	Baldini et al. (2024)
			Baldini et al. (2024)

properties, including acetylcholinesterase inhibitory activity. By altering different components of the molecule, such as functional groups or aromatic rings, insights can be made into the specific structural features that influence the compound's interactions with biological targets. Over the past decades, numerous structure–activity relationship studies have demonstrated that substitutions at positions 1, 2, 3, 7 and 9 of the harmine molecule are either well tolerated or can significantly enhance the biological activity. These studies provide valuable information for optimizing harmine derivatives and identifying key structural elements that increase the benefits of the compound. This review presents the most important biological activities of harmine derivatives, their structural modifications, and their chemical characteristics.

Antitumor potential of harmine derivatives

Harmine and its 9-substituted derivatives (Fig. 3) possess potent anticancer properties attributed to their ability to interfere with the activities of topoisomerase by binding to DNA (Yañuk et al. 2018). Topoisomerases are nuclear enzymes involved in DNA replication, transcription, chromosomal segregation, and recombination. All cells contain two types of topoisomerases: type I enzymes that cut and pass single-stranded DNA and type II enzymes that cut and pass double-stranded DNA. DNA topoisomerases are major targets for both licensed and developing anti-cancer drugs (Nitiss et al. 2012). The inclusion of suitable substituents such as methyl or phenylpropyl at position 9 of the harmine structure is an important element determining the anticancer efficacy of

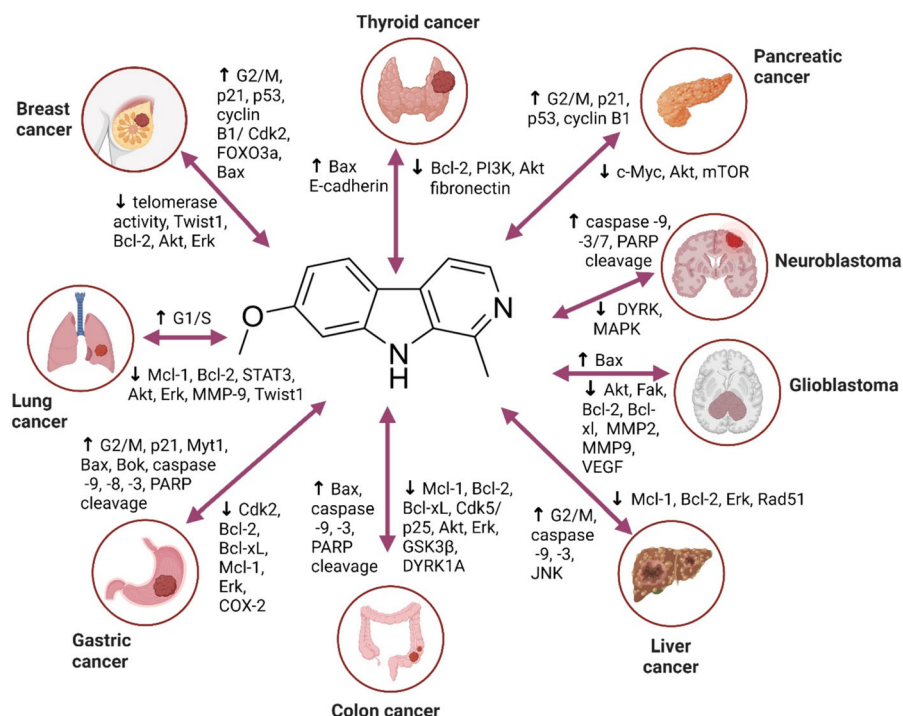


Fig. 2 Illustration depicting the mechanisms of harmine induced activity in different cancer types

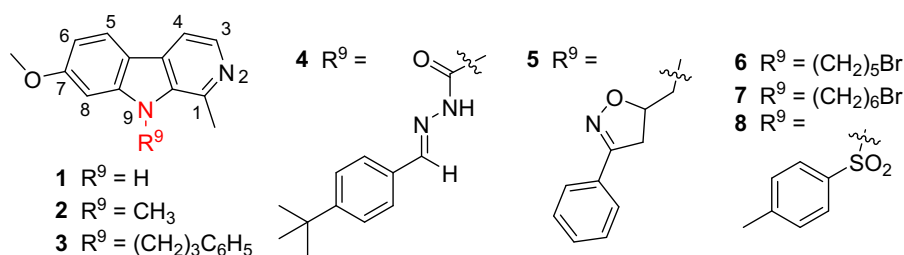
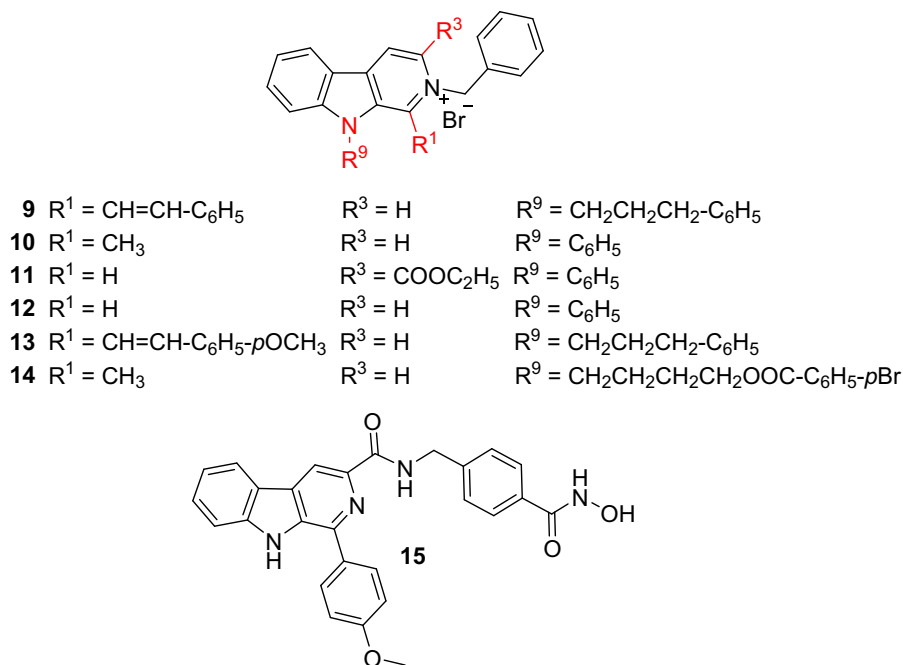


Fig. 3 N9-substituted derivatives of harmine

harmine derivatives. These changes, especially introducing a short alkyl group at position-9 of the β -carboline nucleus, increased harmine's affinity for DNA, resulting in significant inhibitory effects on topoisomerase I, however topoisomerase II is unaffected (Cao et al. 2005b). Topoisomerase I inhibitors are known to cause DNA single-strand breaks, resulting in a buildup of DNA damage and, eventually, cancer cell death. The selective inhibition of topoisomerase I by harmine derivatives makes them promising candidates for targeted anticancer therapies. Since the most intercalating compound corresponded with the most potent topoisomerase I poison and cytotoxic agent, the 9-methyl (2) and 9-phenylpropyl (3)

derivatives of harmine displayed a significant and broader spectrum of cytotoxic activities against the three tumor cell lines examined (human lung carcinoma 95-D, gastric carcinoma SGC7901 and hepatocellular carcinoma HepG2). Moreover, this observation of inhibitory activity against topoisomerase I aligns with the lowest IC_{50} values observed in the study. By selectively targeting topoisomerase I and interfering with its function, derivatives of harmine can disrupt the processes of DNA replication and transcription in cancer cells. This interference hampers the cells' capability to divide and multiply, ultimately leading to their demise. This targeted approach also reduces the potential for off-target

Fig. 4 Modified derivatives of harmine in positions 1, 2, 3, 7, and 9



effects on non-cancer cells and offers a potential strategy for improving cancer treatment efficacy (Cao et al. 2005b).

Also, other research studies have described how substitutions at position 9 of harmine can significantly increase its anticancer activity (Cao et al. 2005a, 2013; Du et al. 2016; Filali et al. 2015, 2016a, 2016b; Chen et al. 2005). The derivatives of harmine with substituents at this location have been revealed to be cytotoxic against cancer cells of different histotypes. Harmine derivatives containing hydrazone substituents (**4**), for example, exhibit high cytotoxicity, with certain derivatives being more inhibitory than harmine itself (Filali et al. 2016a). The addition of a 4,5-dihydro-3-phenylisoxazol-5-yl)methyl moiety at position 9 (**5**) results in strong cytotoxicity against the MCF-7 breast cancer cell line with an $\text{IC}_{50} = 0.2 \mu\text{M}$ at 48 h post-treatment. Conversely, the follow-up cytotoxic tests employing the HCT116 colon cancer cell line model revealed that the derivative **5** exhibited lower cytotoxicity than parent harmine (Filali et al. 2015). Furthermore, substituting either benzenesulfonyl or haloalkyl groups at position N9 substantially increases the anticancer activity of harmine derivatives. The *in vitro* anticancer activity of the synthesized compounds was evaluated within 48 h of treatment using an MTT assay on four human cancer cell lines

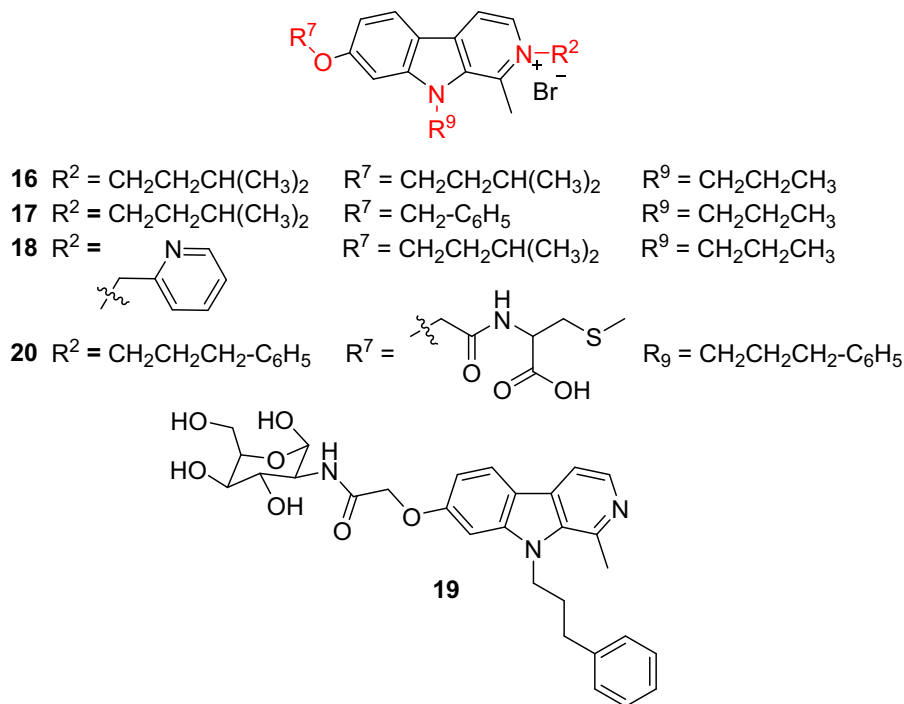
(MCF-7, SGC-7901, SMMC-7721, and A-549). Among the derivatives prepared, the N9-haloalkyl harmine derivatives exhibited either moderate or potent anticancer activity against all tested cell lines. Out of the prepared N9-bromoalkyl derivatives, the 5-bromopentyl (**6**) and 6-bromohexyl (**7**) were the most promising compounds against all tested cell lines, with IC_{50} values of 0.76–9.34 and 0.45–6.94 μM , respectively. Most promisingly, the harmine derivative with 4-methylbenzenesulfonyl at N9 (**8**) was seen to selectively inhibit the growth of A549 cells, with an IC_{50} value of 0.48 μM and was far more potent than the parent harmine ($\text{IC}_{50} = 42.25 \mu\text{M}$). The follow-up investigation of the mechanism in A549 cells revealed that harmine derivative **8** induced dose-dependent (0.1, 0.5 and 1 μM) cell cycle arrest in the G2 phase and triggered apoptotic cell death, as evidenced by Annexin V staining (Du et al. 2016). In summary, the results indicate that the N9-position plays an important role in modulating the anticancer potential of harmine and the short alkyl or aryl substitutions at position 9 result in greater cytotoxicity than long alkyl substitutions, as observed in various cancer cell lines (Chen et al. 2005).

In light of the previous structural activity studies conducted on the N9 derivative of harmine, multiple structural changes at positions 1, 2, 3, 7, and 9 of the

tricyclic, pyridine-fused indole framework of β -carboline were investigated (Fig. 4) (Cao et al. 2013; Miao et al. 2018). Selective substitutions at these sites produced harmine compounds with potent antiproliferative activity against cancer cells. In gastric carcinoma (BGC-823), non-small cell lung carcinoma (A549), liver carcinoma (Bel-7402 and HepG2), malignant melanoma (A375), renal carcinoma (786-0 and 769-P), epidermoid carcinoma of the nasopharynx (KB), colorectal carcinoma (DLD, RKO and HCT116) and colon carcinoma (HT-29), benzenlidene substituted harmine derivatives with replacements at position 1 (**9**) or benzylated quaternary substitutions at position N2 (**9–13**) demonstrated high cytotoxic activity with IC_{50} values in the low micromolar range (Cao et al. 2005a, 2013; Zhang et al. 2016b). Besides, the most potent 1-benzenlidene, N2-benzyl substituted harmine derivative **13** caused a significant increase in apoptosis, ROS overproduction and inhibition of Akt phosphorylation. The apoptotic activity has been demonstrated to be induced at a lower level of concentration, being considerable from 5 μ M of compound **13**. This was associated with an initial increase in ROS production, which served as an upstream event and facilitated the inhibition of Akt phosphorylation. Consequently, this triggered the cell apoptosis via the mitochondrial pathway. Subsequent *in vivo* experiments demonstrated the tumor-inhibiting effects of compound **13**. Treatment with derivative **13** resulted in the inhibition of tumorigenesis in the colorectal cancer cell line HCT116 in nude mice, with a noticeable reduction in tumor volume by day 13 compared to the DMSO control group (Zhang et al. 2016b). The derivatives of harmine with benzyl substitutions at position N2 and arylated alkyl substitutions at position N9 (**14**) inhibit MDA-MB-231 triple-negative breast carcinoma, A549 lung adenocarcinoma, U2OS osteosarcoma, and PANC-1 pancreatic cancer cell lines while having only a minor effect on normal lung fibroblast HLF α . The most active N2,9-disubstituted harmine derivative **14** also preferentially induced apoptosis and inhibited autophagy. While compound **14** proved to be the most effective in inhibiting the growth of cancer cells in non-small A549 lung adenocarcinoma cells, it had only a mild effect on perturbing the cell cycle, resulting in a moderate accumulation of A549 cells in the S phase after 24 h of treatment. Because harmine derivative **14** contains an ester modification, a

potential concern for future drug development is its stability inside cells. However, using UPLC-Q-TOF-MS analysis, the researchers demonstrated that compound **14** remains stable within cells *in vitro*. Furthermore, Geng and coworkers give arguments and data indicating that harmine and its analogs failed to induce Chk1 phosphorylation, suggesting that DNA intercalating and topoisomerase inhibition are unlikely involved in the cytotoxicity of these compounds (Geng et al. 2018). In 2018, an array of hybrids made up of the essential structural components of hydroxamic acid and β -carboline, the phenyl ring of traditional histone deacetylase (HDAC) inhibitors was swapped out for an aromatic heterocyclic ring of β -carboline. Harmine derivative N-(4-(hydroxycarbamoyl)benzyl)-1-(4-methoxyphenyl) is one of them. Indole-3-carboxamide [3,4-b]-9H-pyrido (**15**) not only shown strong antiproliferative activity against the human cancer cell lines, Hep G2, Huh7, SMMC-7721, HCT116, H22, and H1299, but it also demonstrated *in vitro* specific inhibitory actions of HDAC1/6 class I and II. Furthermore, this harmine analogue containing substitution on C-1 and C-3 simultaneously increased the acetylation of histone H3, H4, and α -tubulin, consequently triggering significant cancer cell apoptosis and cell cycle arrest at G2/M by inhibition of both Cdk1 and cyclin B in a concentration-dependent manner. Harmine derivative **15** effectively suppresses the invasion and migration capabilities of highly metastatic hepatocellular carcinoma HepG2 cells. This is achieved through the downregulation of the expression of tumor metastasis-related proteins MMP-9 and MMP-2 in a concentration-dependent manner. Notably, **15** exhibited low acute toxicity and demonstrated significant growth inhibition of hepatoma tumors *in vivo* (Miao et al. 2018). These results indicate that introducing suitable substituents at positions 1, 2, 3, 7, and 9 can augment the anticancer potential of harmine (Cao et al. 2013; Miao et al. 2018).

Trisubstituted harmine derivatives (Fig. 5), characterized by molecular structural alterations at positions 2, 7, and 9, have emerged as a promising area in cancer research. Extensive efforts have been directed toward their synthesis and assessment over the last decade, providing a multitude of studies (Carvalho et al. 2017; Frédérick et al. 2012; Guo et al. 2014; Li et al. 2015; Marx et al. 2019; Meinguet et al. 2015). The derivatives have improved anticancer efficacy

Fig. 5 Trisubstituted derivatives of harmine

against a variety of cancer cell types. However, efforts have been made to enhance their solubility and optimize their structures. Harmine derivatives with minor substituents like propyl, isopentyl, or benzyl moieties (**16**, **17**), for example, have been created to enhance solubility while maintaining anticancer action (Meinguet et al. 2015). In glioma cell lines (Hs683, T98G and U373) and esophageal cancer cell lines (OE33, OE21), several trisubstituted harmine derivatives (**16**, **18–20**) displayed greater solubility and significant anticancer effects (Carvalho et al. 2017; Li et al. 2015; Marx et al. 2019). In a study by Li et al. 2015, modification of harmine was found to improve its therapeutic efficiency and reduce systemic toxicity. This was accomplished by synthesizing two harmine derivatives, 2DG-Har-01 (**19**) and MET-Har-02 (**20**), both of which were modified to target cancers. Strategic substitutions were made at positions 2, 7, and 9 of the harmine ring, resulting in two different targeting groups: 2-amino-2-deoxy-D-glucose (2DG) and methionine (Met). According to the findings of this investigation, these novel harmine derivatives had much higher therapeutic effectiveness than harmine (Li et al. 2015). Li et al. 2015 further investigated the anticancer properties of 2DG-Har-01 and MET-Har-02 on the human cancer cell lines (LoVo, SMMC-

7721, MCF-7, HuH7, and HepG2). In this experiment, they used the original harmine and, as a control substance, the anticancer drug 5-fluorouracil (5-fu). The results exhibited dose-dependent anti-tumor activity of the modified harmine derivatives across various concentrations. 2DG-Har-01 exhibited enhanced antitumor effects compared to harmine controls on SMMC-7721 and LoVo cells, whereas MET-Har-02 displayed superior antitumor activity compared to both harmine and 5-fu across all cell lines, with particularly remarkable effects on HuH7 and SMMC-7721 hepatocellular carcinoma cells (Li et al. 2015).

Researchers used HepG2 cells in a clone formation assay to learn more about the effects of MET-Har-02 and harmine on cancer cells. After seven days of exposure to specific doses of MET-Har-02 and harmine, the number of generated clones was significantly reduced in contrast to the control group. Notably, at a concentration of 5 μM , both MET-Har-02 and harmine inhibited HepG2 cell colony formation, with MET-Har-02 suppressing colony formation more than harmine.

Moving from in vitro to in vivo studies, Li et al. 2015 evaluated the anti-tumor efficiency of 2DG-Har-01 and MET-Har-02 in mice with S180 tumors (a

murine sarcoma cancer cell line). Amazingly, all treatment groups, including those administered with 2DG-Har-01, MET-Har-02, and harmine, showed a significant reduction in tumor growth compared to the saline-injection vehicle control group. With a tumor inhibition ratio of 67.86%, MET-Har-02 surpassed 2DG-Har-01 (42.84%) and harmine (30.93%) among these treatments. In vitro and in vivo tests were performed to determine the neurotoxicity profiles of 2DG-Har-01, MET-Har-02, and harmine. During the ten-day observation period, healthy mice given varied dosages of 2DG-Har-01 and MET-Har-02 (10, 50, 100, 200, and 500 mg/kg, i.p.) showed no symptoms of neurotoxicity, such as tremors, tetanus, twitching, leaping, supination, or death. Mice given 100 mg/kg harmine, on the other hand, demonstrated acute neurotoxic behaviors. Cell survival rates verified these findings, with the harmine-treated group exhibiting a survival rate of 39%, while the 2DG-Har-01 and MET-Har-02-treated groups exhibited survival rates of 80% at a drug concentration of 200 μ M. These findings imply that the modified harmine derivatives, 2DG-Har-01 and MET-Har-02, have less neural toxicity than parent harmine (Li et al. 2015).

Conclusion

In conclusion, harmine emerges as a versatile and potent candidate in the fight against cancer. This natural chemical has shown great anticancer potential through a variety of mechanisms. Harmine's intricate molecular effects are highlighted by its capacity to bind to DNA and cause damage by intercalation. In addition, harmine's suppression of the NF- κ B signalling pathway inhibits tumour angiogenesis by lowering the production of proangiogenic molecules such as VEGF, NO, and various other factors like IL-2, MMPs, COX-2, and inducible nitric oxide synthase. Its effectiveness in halting the growth and spread of malignant tumours is demonstrated by this activity. Harmine has demonstrated its ability to suppress cancer cells by coordinating multiple complex mechanisms. Its activation of Myt1, phosphorylation and deactivation of Cdk2, and overexpression of p21, which results in G2 phase cell cycle arrest, are examples of how it causes apoptosis and inhibits proliferation. Among harmine's outstanding antiproliferative and cell viability effects is the stimulation of

mitochondrial-related apoptosis through the regulation of the Erk/Bad and caspase-8/Bid pathways. Harmine successfully tips the scales in towards programmed cell death within malignant cells by controlling the expression of important actors like Bcl-2, Mcl-1, Bax, Fas, and caspase 3/– 9. Harmine's status as a powerful anti-cancer agent is further supported by its capacity to inhibit DYRK1A protein kinase and Cdks. Furthermore, harmine's interaction with DYRK1A causes cancer cells to undergo apoptosis and activate caspase-9, opening up new therapeutic options. The dynamic research field of harmine derivatives and structural alterations is opening up new avenues for cancer research. Through deliberate structural modifications of harmine and the addition of appropriate substituents at particular positions, scientists have discovered new molecules with improved anticancer properties. With substitutions at positions 2, 7, and 9, trisubstituted harmine derivatives have a lot of potential to further our knowledge of harmine's anticancer effects. Furthermore, harmine has a synergistic anticancer impact when used in conjunction alongside conventional chemotherapy drugs. This cooperative method exhibits great promise for improving the effectiveness of cancer medicines, particularly in situations like pancreatic and stomach cancer, where harmine has proven to be compatible with current treatments.

Given these results, harmine represents a ray of hope in the search for potent anticancer therapies. The need for more research is highlighted by its diverse modes of action, creative structural alterations, and potential in combination therapy. Despite its potential, harmine and its derivatives have been linked to reported adverse effects, including neurotoxicity, according to animal research involving mice. These investigations provide noticeable evidence of acute toxic consequences after harmine exposure, such as tremors, twitching, jumping, tetanus, and supination. Additionally, there is a suggestion that harmine's neurotoxic effects may lead to cognitive decline and memory issues. However, it is critical to note that additional research is required to fully investigate and comprehend the consequences in this area. The potential relevance of harmine in cancer therapy is growing as we learn to understand its complex mechanisms. The path towards achieving harmine's maximum potential has the potential to revolutionize cancer therapy.

Acknowledgements This work was supported by the Cooperatio Program, research area DIAG and SVV-2023-260656 of Charles University. BioRender software was used to prepare some of the schematic figures (BioRender.com).

Declaration

Conflict of interest The authors declare no conflict of interest.

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